

TRC105 for the treatment of Hepatocellular Carcinoma: Preclinical data and preliminary results from two clinical trials evaluating monotherapy and combination with sorafenib.

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Introduction

Sorafenib is an oral multi-kinase inhibitor of vascular endothelial growth factor (VEGF) receptor, the platelet-derived growth factor (PDGF) receptor, and Raf and was the first systemic medical therapy to prolong survival in HCC based on the SHARP study which demonstrated a median overall survival benefit compared to placebo (10.7 months v 7.9 months; HR 0.69; P<0.001). Since the SHARP study, attempts to combine agents with sorafenib have been disappointing.

Endoglin (CD105) is a transmembrane receptor overexpressed by proliferating endothelial cells that is required for angiogenesis and upregulated by hypoxia in response to VEGF inhibition. TRC105 is a chimeric IgG1 monoclonal antibody that binds CD105 with high avidity and inhibits binding of its key ligand, bone morphogenic protein. TRC105 inhibits angiogenesis and mediates apoptosis and antibody-dependent cell-mediated cytotoxicity (ADCC) of proliferating endothelium.

Methods

Preclinical studies: We first performed a preclinical study to evaluate a surrogate antibody to mouse endoglin as a single agent and in combination of sorafenib. Murine BNL HCC cells were grown subcutaneously in Balb/c mice and mice were then treated with antibody to murine endoglin, (clone MJ7/18; 10-200ug) ± sorafenib (10 mg/kg daily p.o.) or sorafenib alone.

Clinical trials: Patients with HCC and compensated liver function (Childs Pugh A/B7), ECOG 0/1, were enrolled in two studies: (1) a phase I study of TRC105 given at 3, 6, 10, 15mg/kg every 2wks plus sorafenib 400mg bid; and (2) (in sorafenib refractory or intolerant patients) a phase II study of TRC105 at 15mg/kg q 2wks. Correlative biomarkers evaluated included DCE-MRI; FDG-PET; color Doppler ultrasonography; circulating endothelial and endothelial progenitor cells, plasma levels of angiogenic factors; soluble endoglin and tumor IHC for endoglin. Immunogenicity studies were also performed.

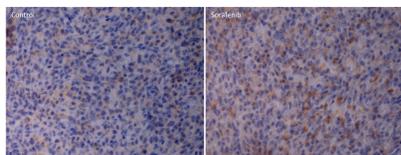


Figure 1: Detection of endoglin expression in BNL hepatocellular tumors growing subcutaneously and treated with sorafenib.

Results (1): Analysis of CD105 expression after sorafenib treatment.

BNL tumors were grown in Balb/c mice and sorafenib was initiated at a dose of 10 mg/kg daily. Tissue was harvested after 3 days and analyzed by immunohistochemistry. As shown in Figure 1, sorafenib treatment induced an increase in endoglin expression in subcutaneous BNL tumors, compared to control mice who did not receive sorafenib.

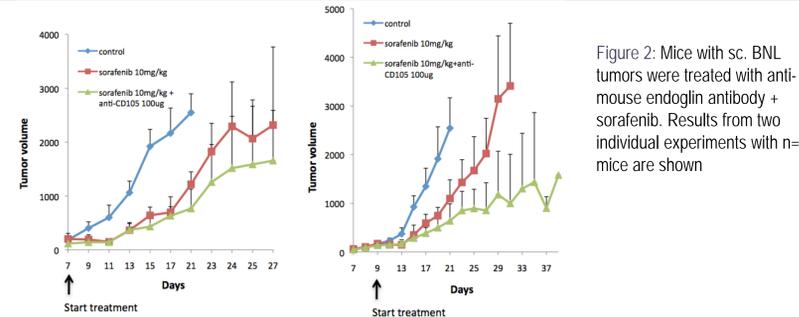


Figure 2: Mice with sc. BNL tumors were treated with anti-mouse endoglin antibody + sorafenib. Results from two individual experiments with n=5 mice are shown

Results (2): Effect of anti-mouse endoglin antibody (clone MJ7/18) on tumor growth in combination with 10 mg/kg sorafenib daily. Based on the observation that endoglin expression was increased in tumors of mice treated with sorafenib, we tested the combination of anti-mouse endoglin antibody + sorafenib in two independent experiments. As shown in Figure 2 the combination of anti-CD105 + sorafenib was more effective than sorafenib treatment alone.

Characteristic	No. of pts	No. of pts
	Phase 1	Phase 2
HCC	11	9
FLHCC	1	1
Sex		
Male	8	8
Female	4	2
Age, years		
Mean	52	53
Range	18 - 69	24-67
Cirrhosis		
Yes	6	6
no	6	4
Hepatitis B	2	2
Hepatitis C	6	5
Administered cycles		
Mean	4.75	2
Range	2- 10	1-3
Best Response		
CR	0	0
PR	1	0
SD	3(>6/12)	3
PD	3	4
Not evaluable/clinical progression	4	3

Table 1: Patient characteristics

Toxicity (Grade ≥ 3)	Phase 1			Phase 2 (N=10)
	3mg/kg (N=3)	6mg/kg (N=3)	10mg/kg (N=6)	
Anemia			1	2
Hand-foot syndrome	1	1	4	
Hypophosphatemia	1			
Hyperbilirubinemia	1	1		
AST/ALT elevation	1		2	3
Diarrhea	1			
Intracranial hemorrhage		1		
Lymphopenia			2	3
Cardiac ischemia			1 (G5)	1

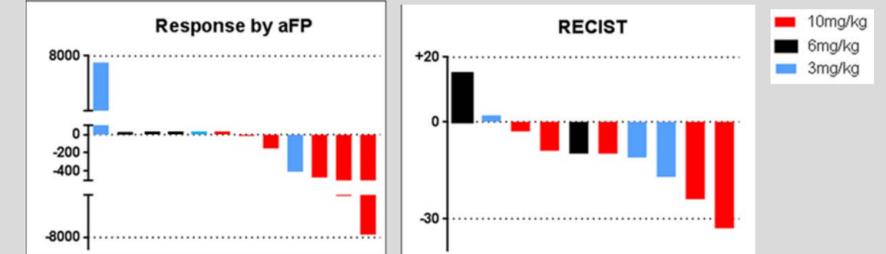
Table 2: Toxicity data

Results (3): Clinical trials:

22 pts have been treated in total so far; M:F 16:6; Mean age = 52 (range 18-67); see Table 1. **Phase I: TRC-105 with sorafenib (N=12):** 1 DLT (increased AST) occurred at 10mg/kg and dose escalation is ongoing at 15 mg/kg of TRC105. The most frequent toxicity has been epistaxis. One patient with coronary stenosis developed a fatal myocardial infarction and one patient with thrombocytopenia developed G3 cerebral tumor hemorrhage. At a site of metastasis Efficacy data are shown below. One patient (FLHCC) treated at 10mg/kg dose level developed a PR by RECIST and the majority of patients had tumor reduction. Median time on study was 4 months and one patient remains on treatment after 16 months.

Phase II TRC-105 alone (N=10): No grade 3/4 treatment-related toxicities were observed. Most frequent toxicities were headache (G2; N=3) and epistaxis (G1; N=4). One patient with a history of ischemic heart disease developed an acute cardiac syndrome following a hypertensive episode during the first infusion, and recovered without surgical intervention. Efficacy data are shown below. Two patients were progression free at 4 months by RECIST. Median time on study was 2 months. Preliminary evidence of biologic response was seen on DCE-MRI in 1pt (of 3 evaluable) with a reduction in kTrans and kep and 3pts (of 3 evaluable) who demonstrated reduction in intra-tumoral color flow on color Doppler.

Efficacy: Phase I of TRC105 + sorafenib



Efficacy: Phase II of TRC105 alone



CONCLUSIONS:

TRC105 is well tolerated both as single agent and when combined with sorafenib. Evidence of biological and clinical activity was observed as a single agent and when combined with sorafenib. Based on preclinical data and activity of the combination, future studies of TRC105 and sorafenib in HCC are planned.